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Chapter 20: Issues in planning cervical cancer screening in the era of HPV vaccination

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Abstract

Human Papillomavirus (HPV) vaccines will likely have an impact as a preventive strategy for cervical cancer. Screening for precancerous lesions cannot be discontinued because vaccination will not protect against HPV types not included in the first generation of vaccines. Moreover, protection for the target types, 16 and 18, which are responsible for most cases of cervical precancerous lesions and cancer, and 6 and 11, which are responsible for a substantial proportion of low-grade lesions, cannot be expected to be absolute, and the likely implementation of HPV vaccination in young women will not impact older groups initially. Cervical cancer control programs will need to be re-evaluated because the addition of HPV vaccination will make the existing approach of high-frequency screening by cytology too costly and inefficient for most public health budgets. Simply making cytology screening less frequent may not be a viable strategy in light of potential problems that may plague cytology performance in conditions of low lesion prevalence. HPV testing has the performance characteristics that would make it an ideal primary screening test in such conditions. Cytology should be reserved for triage of HPV-positive cases because it is more likely to perform with sufficient accuracy in high-prevalence conditions. Another advantage of using HPV testing as a primary screening tool is the opportunity to create infection registries that can link test results from the same women over time, thus allowing an efficient and low-cost strategy to monitor long-term protection among vaccinated women.

Keywords: Cervical cancer; HPV; Vaccines; Screening; Cytology; Prevention

1. Introduction

Initial results with the candidate HPV virus-like particle (VLP) vaccines indicate that protection against persistent infection with HPV types 16 and 18 is nearly 100% in up to 5 years of follow-up [1–4]. Ongoing phase-III studies are likely to corroborate these findings and show high vaccine efficacy against high-grade preneoplastic cervical lesions. Mathematical models of the impact of HPV vaccines have also projected a substantial public health benefit in most geographical areas [5–7]. In light of the promising results thus far, applications have been made by two pharmaceutical companies, Merck and GSK, to license and commercialize their respective candidate vaccines to prevent cervical lesions caused by the target HPV types that are responsible for the majority of cervical cancers, namely HPV-16 and -18.

2. Opportunities for cervical cancer control

Fig. 1 shows the phases in any cancer control program and the phase-specific outcomes as they apply specifically to cervical cancer prevention. Of the primary prevention

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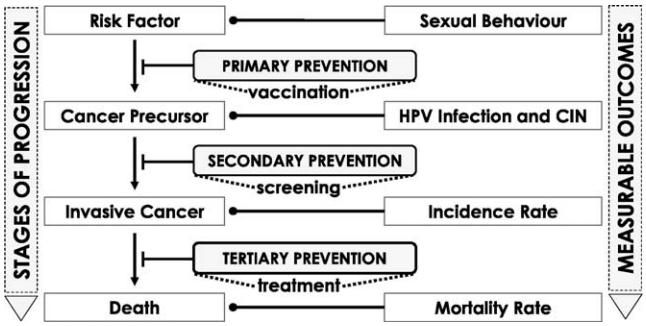

Fig. 1. Schematic illustration of opportunities for cancer control interventions are provided by the illustrated stages of progression on the left and measurable outcomes on the right which apply to cervical cancer prevention via HPV vaccination (primary), screening with Pap cytology and HPV testing (secondary), and treatment (tertiary).

strategies for cervical cancer, HPV vaccination is the one most likely to succeed. Pap cytology screening followed by the triage of cases of abnormal cytology and management of confirmed precancerous lesions has been the mainstay of secondary prevention for cervical cancer for over half a century. Stage- and prognostic-factor-tailored treatments are the main approaches in tertiary prevention. Although there has been much progress in the latter phase, it is essentially the combination of primary (HPV vaccination) and secondary (screening) prevention strategies that form the basis for further reducing incidence of, and mortality from, this second most common cancer of women worldwide.

3. Impact of HPV vaccination on existing cervical cancer prevention programs

Perhaps one of the most neglected aspects of the ongoing debate on the potential impact of prophylactic HPV vaccination is the need to examine existing screening practices to permit synergy between primary and secondary prevention efforts. Assuming that HPV vaccination will become an accepted primary prevention approach, it is essential to consider what to do with the prevailing secondary prevention strategy, i.e., screening with Pap cytology.

3.1. The cytology screening paradigm

Organized or opportunistic screening with Pap cytology has been the primary reason for the substantial reductions in cervical cancer morbidity and mortality during the last 50 years in high- and middle-income countries. However, the economic burden imposed by Pap screening is substantial. In most Western countries, for example, for each new case of invasive cancer found by cytology there are approximately 50–100 other cases of precursor lesions, such as squamous intraepithelial lesions (SIL) of low-grade (LSIL) and high-grade (HSIL), that require clinical management to prevent progression to invasive cancer. To this burden, one must add twice as many cases of equivocal or borderline atypias, also known as “atypical squamous cells of undetermined significance” (ASCUS). ASCUS and SIL findings account for up to 10% of all Pap smears that are processed in screening programs in Western countries [8].

Pap cytology is based on a highly subjective interpretation of morphologic alterations present in cervical samples. The highly repetitive nature of the work of screening Pap smears leads to fatigue, which causes interpretation errors. A meta-analysis that included only studies unaffected by disease verification bias indicated that the average sensitivity of Pap cytology to detect cervical intraepithelial neoplasia (CIN) or cancer was 51% and its average specificity was 98% [9]. Therefore, the Pap test’s high false-negative rate has been its most critical limitation. False-negative diagnoses are attributable to slide reading errors and to poor sample collection and slide preparation. The advent of liquid-based cytology has contributed to mitigating the problem of efficiency in processing smears, but the limitations of cytology remain the same. This low sensitivity for an individual test has to be compensated by the requirement to have women entering screening age with an initially negative smear to repeat their tests at least twice over the next 2–3 years before they can be safely followed as part of routine screening. This brings the program sensitivity to acceptable levels but safeguards must be in place to ensure compliance, coverage, and quality; costly undertakings that have worked well only in Western industrialized countries. Many developing countries that have invested in screening programs have yet to witness a reduction in cervical cancer burden [10].

3.2. Implementation of HPV vaccination

Adoption of prophylactic HPV vaccination is likely to be a gradual process that will reflect country-specific health-policy environments. In some jurisdictions, vaccination may be adopted as a universal policy for all young women and covered by a centrally managed healthcare system. In other settings, the costs of vaccination may be shared between the public sector and individuals, based on categories of risk defined by immunization advisory committees serving ministries of health or other governmental bodies. It is also conceivable that some countries may not opt for covering vaccination costs at all and may leave the decision to health providers and patients. Finally, it is also likely that due to other pressing healthcare priorities some countries may not even adopt vaccination. The diversity in implementation scenarios is thus likely to be substantial. Nevertheless, they will likely reflect individual countries’ perceptions regarding the cost-effectiveness of vaccination. To be well informed, such decisions must imply that consideration was given to whether or not existing screening programs are to be modified to improve the cost-effectiveness of vaccination.

The two candidate vaccines that are likely to be licensed in 2006 and 2007, Merck’s Gardasil® and GlaxoSmithKline’s Cervarix®, do not protect against all HPV types that cause

cervical cancer, although some degree of cross-protection against other oncogenic HPVs may be observed. There is also the potential for the distribution of HPV types in vaccinated populations to change gradually as a reflection of the vacated ecologic niches following the progressive elimination of HPV-16 and -18 (an as-yet unproven phenomenon also known as type replacement). There is also the possibility that the type-specific immunity conferred by vaccination may wane over periods extending at least beyond 5 years.

While much is yet to be learned about these and other vaccine-related issues, such as target ages and whether or not men should be vaccinated, it is sensible to consider that incorporation of HPV vaccination cannot be cost-effective without substantial changes to existing screening policies. Even resource-rich countries will be hard pressed to absorb the high societal costs of vaccination without some form of streamlining or restructuring their screening programs. The issues that are likely to arise and plausible outcomes of screening in the new era of HPV vaccination are outlined in the next section.

4. Possible immediate public health outcomes of HPV vaccination

Women receiving the full three-dose course of one of the two candidate HPV vaccines will have much lower rates of ASCUS and SIL. It is thus sensible to assume that the rates of colposcopical referral will decrease substantially to perhaps 60% or less of the existing case loads in most Western countries [4,11]. A small proportion of such abnormalities are associated with the low-risk types 6 and 11. Merck's quadrivalent vaccine includes the latter two types and may thus lead to a further reduction in abnormalities, perhaps by an extra 10%. These reductions will translate into initial savings to the healthcare system or to individuals but may entail undesirable consequences related to personnel training and degradation of performance for Pap cytology (discussed elsewhere in this chapter).

The most obvious impact of vaccination is in preventing infections with the target types. HPV testing has been recommended in some jurisdictions as an adjunct test with Pap cytology for women older than 30 years of age. Guidelines in many industrialized countries have recently incorporated HPV testing via the Hybrid Capture™ assay as a colposcopy triage tool for women with ASCUS smears. Data from the ASCUS and LSIL (ALTS) trial in the US indicate that approximately 55–60% of ASCUS smears and nearly 90% of LSIL smears are positive for oncogenic HPV types. By eliminating abnormalities caused by HPV-16 and -18, which are the clearly more aggressive types [12,13], vaccination could permit more conservative management practices in the future. Approximately 20–30% of LSIL and ASCUS smears harbour HPV-16 and/or -18 [11].

The extent of the above reductions in case loads will primarily be a function of two factors: (i) the overall uptake of HPV vaccination, and (ii) the time it will take for protected women to reach the age when they become screening clients. In countries without a centrally managed healthcare system, such as the United States, high vaccination uptake will require much effort in educating the public and health providers. While women may welcome HPV vaccines there may be dissent as well, stemming from the perception that vaccination may foster permissive behaviour among adolescents [14,15]. Surveys of health providers show high acceptance rates, particularly if professional societies provide endorsement [16].

Protection of women between the ages of 10 and 25 years is the likely initial target of HPV vaccination. Vaccinated adolescents will reach screening age within 3 years after becoming sexually active, therefore, the impact on screening and management case loads will be initially minimal for women vaccinated before the age of 18 years. On the other hand, the benefits in risk reduction among young adult women (e.g., ages 20 and older) receiving the vaccine will be realized almost immediately because of the short latency between averted HPV infection and appearance of cervical abnormalities.

5. Possible long-term public health outcomes of HPV vaccination

Even with high vaccination uptake, a reduction of cervical cancer burden is unlikely to be observed for at least a decade, or longer, because of the latency required for averted HSILs to have had the time to progress to invasive disease. In settings without centrally funded universal vaccination, a high vaccine uptake could be primarily among women who would eventually be compliant with screening. A paradoxical situation may thus arise: if adolescents and young women who are more likely to be vaccinated are the very ones destined to become screening-compliant, the reduction in precancerous lesions will be seen nearly exclusively among such women. There may be initial perceptions of success with the reduction in case loads on screening of these women. However, because of their high screening compliance they would not have developed cervical cancer. On the other hand, in opportunistic screening settings, non-vaccinated women may be less likely to be screened and their lesions will progress undetected until invasion occurs. No precancerous lesions will be averted and cytology surveillance will be oblivious to their existence until invasive cancer develops and the attendant symptoms will then prompt the need for diagnosis.

5.1. Loss of screening performance due to vaccination

In the post-vaccination era, one would expect that today's critical problem of false-negative diagnoses (i.e., a lack in sensitivity) would not be as pronounced, unless other pitfalls occur. On the other hand, the reduction in prevalence of squamous abnormalities will lead to a decrease of the positive predictive value (PPV) of Pap cytology, a parameter that

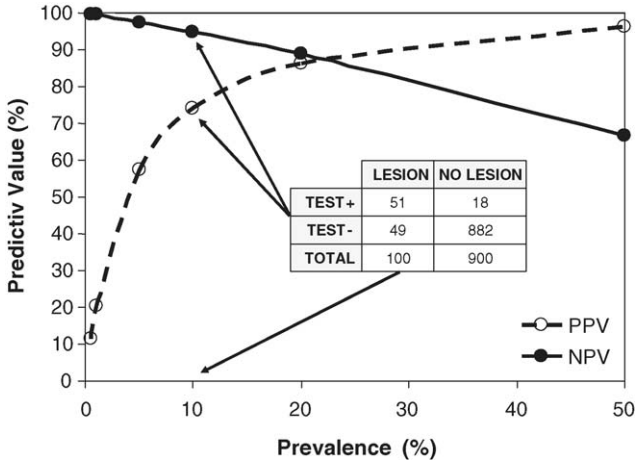

Fig. 2. Influence of variations in lesion prevalence (0.5, 1, 5, 10, 20, and 50%) on the positive predictive values (PPV) and negative predictive values (NPV) for cytology, assuming constant 51% sensitivity and 98% specificity (the average estimates in studies free of verification bias [9]). The inset table shows an example of possible results in a sample of 1000 women in whom prevalence of lesions is 10%. The corresponding PPV and NPV are 73.9 and 94.7%, respectively. The formulas used for PPV and NPV are: $PPV = Sens \times Prev/[Sens \times Prev + (1 - Spec) \times (1 - Prev)]$ and $NPV = Spec \times (1 - Prev)/[(1 - Sens) \times Prev + Spec \times (1 - Prev)]$.

indicates how correct a positive result would be in triggering management. As PPV decreases with reductions in prevalence, increasingly larger proportions of women who screen positive will in fact have a false-positive diagnosis that could result in unnecessary worry and medical interventions. Management options for an ASCUS or LSIL abnormality include immediate colposcopy referral, a repeat Pap test, HPV testing triage (for ASCUS), or an intensification in screening frequency (for ASCUS). These decisions lead to substantial costs to the patient or health-care system and cause anxiety to patients and their families.

Fig. 2 illustrates this problem by showing the influence of the prevalence of underlying cervical lesions on the PPV and negative predictive value (NPV) by cytology, assuming that it performs at a constant 51% sensitivity and 98% specificity [9]. The six lesion prevalence rates shown (0.5, 1, 5, 10, 20, and 50%, corresponding to PPVs of 11.4, 20.5, 57.3, 73.9, 86.4, and 96.2%, respectively) reflect the situations expected post-vaccination as well as those currently seen in different settings. For instance, in unscreened populations of Africa and Latin America prevalence of cervical lesions is high, in the 10–20% range. In Western countries abnormality rates are in the range of 5–10%. The 50% prevalence point is used to represent the artificial situation found in triage following an initially positive Pap smear or HPV test.

5.2. Possible qualitative changes in Pap cytology reading performance

The above quantitative effect caused by the decrease in lesion prevalence assumes that cytology will perform with constant sensitivity and specificity regardless of setting. However, we must consider that independent additional factors may contribute to further degrade the PPV of cytology. The reduction in lesion prevalence may have an impact on the performance of cytology because of this test's inherent characteristics and the ensuing change in the signal-to-noise ratio in the pleomorphic cellular abnormalities that cytotechnicians differentiate on a routine basis.

With otherwise constant conditions, the PPV of an abnormal smear will decrease from present-day estimates of 50–70% to 10–20% in settings where most women being screened have received vaccination. A typical cytology laboratory associated with opportunistic or organized screening in most well-served populations has a case load where approximately 10% of all smears contain abnormalities that are deemed serious enough to merit review by a senior cytotechnician or cytopathologist before a diagnosis can be made. In other words, one in every ten smears will trigger the cytotechnician's interest, who will then flag the abnormalities in the slide for review and/or discussion with a supervisor. In a day's batch of 50–100 slides there will always be a few (5–10) to break the tedious work of reading many unremarkable slides. With a reduction in lesion prevalence, fatigue may set in more quickly given the expectation that abnormalities will be rare, a phenomenon that is likely to build slowly as more women are vaccinated. This could have a negative impact on sensitivity because smears may not be read as thoroughly and attentively as before, which would lead to more false-negative diagnoses and consequent losses in sensitivity. In fact, the Pap test's sensitivity can be lower than the above average (51%) in low-risk areas in which the female population is compliant and overly screened [9,17]. Estimates as low as 35% were observed in Newfoundland and Quebec, Canada, in settings with stringent quality-control standards and adequate personnel training [18,19].

On the other hand, with the reduced prevalence of squamous abnormalities and koilocytotic atypias (the "signal" alluded to above), it is possible that cytotechnicians may begin to give more importance to inflammatory changes or reactive atypias (the "noise" alluded to above). This situation may arise not only as an independent factor in performance, but it may also be aggravated by the cytotechnician's fear that relevant abnormalities will be missed. Heightened awareness of the potential for false-negative diagnoses may lead to more false-positive reports and consequently a loss in specificity. The end result is a further decline in the PPV of cytology.

The above two scenarios that negatively affect the sensitivity and specificity of Pap cytology are likely to operate cumulatively with a decrease in lesion prevalence. Fig. 3 illustrates the combined effect of these two scenarios on the PPV over a wide range of sensitivity (ranging from 30 to 95%) and specificity (95, 85, and 75%) values for the same lesion prevalence conditions (0.5, 1, 5, 10, 20, 50%) shown in Fig. 2. As one moves from the highest to the lowest prevalence rates in Fig. 3 the interpolated PPV of cytology may result from

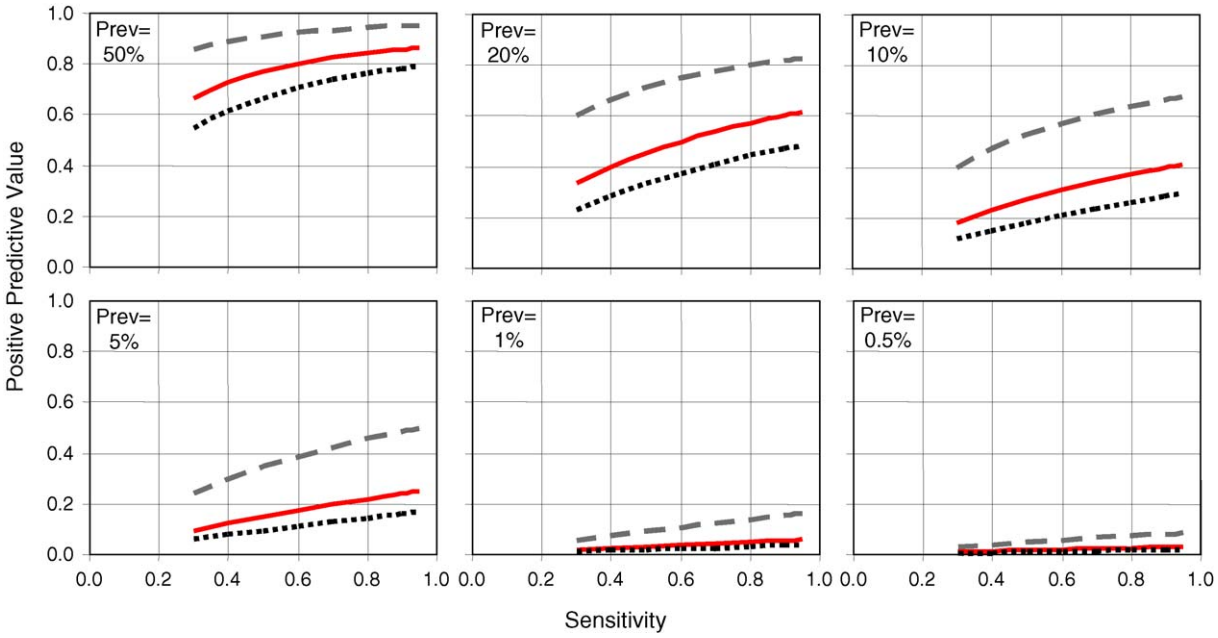

Fig. 3. Joint effects of changes in sensitivity, specificity, and lesion prevalence on the positive predictive value of a screening test. The three curves in each graph represent different specificity estimates (dashed line: 95%; solid line: 85%; dotted line: 75%). From top left to bottom right, the six graphs represent decreasing hypothetical situations of lesion prevalence (prev). These combinations reflect the situations found in Pap cytology screening in different settings as well as the ones anticipated post-vaccination. For instance, in unscreened populations of Africa and Latin America prevalence of cervical lesions is high, in the 10–20% range. In most Western countries abnormality rates are in the range of 5–10%. A 50% prevalence is shown to represent the situation found in triage, following an initially positive referral Pap smear or HPV test.

a shift to the left in sensitivity in curves referring to successively lower specificity.

The type of setting also contributes to the above combination of likely scenarios that may arise as a consequence of the effects of vaccination. Cytology laboratories in litigation-prone countries, such as the United States, will tend to err on the side of conservatism to decrease the risk of malpractice suits. Other settings may rely on maintaining unnecessarily frequent screening visits as policy to provide protection against false-negative diagnoses. Either approach is a non-cost-effective way of exploring the advantages of vaccination in restructuring screening programs.

6. Advantages of an algorithm based on screening for HPV and cytologic triage

There has been substantial interest in the use of HPV tests for two main purposes in early detection: population screening and triage (see Chapters 9 and 10). The evidence in favour of HPV testing in screening is substantial. HPV testing has, on average, 20–40% greater sensitivity but about 5–10% lower specificity than Pap cytology for detecting high-grade lesions or cancer [10,17,20]. The concern with using HPV tests in screening is in increasing the number of colposcopy referrals because of the lower specificity. On the other hand, once HPV-positive women are verified to be lesion-free via colposcopy, an extra margin of safety has just been gained compared with the same assurance had the case detection been prompted by a positive cytology.

HPV testing is based on a highly standardized and validated assay system that suffers from none of the vagaries that typically affect the performance of Pap cytology, except for specimen quality. The pitfalls described above that are likely to affect the performance of cytology resulting from the decrease in lesion prevalence will also affect the PPV of HPV testing, although to a lesser extent. HPV testing is not prone to subjective interpretation and will thus maintain its performance characteristics under low lesion prevalence conditions. The PPV of HPV testing may thus be proportionally higher than that of Pap cytology as lesion rates decrease in response to vaccination, as we move from the high to the low lesion prevalence conditions in Fig. 3.

Although empirical evidence for the above predictions is lacking, it is plausible to expect that cytology may always perform more accurately whenever lesion prevalence is high, which is the situation that is artificially created in triage. On the other hand, the robust performance of HPV testing and higher sensitivity would make it a better screening test in a wide range of lesion prevalence conditions. Cytology's high specificity is ideally suited to rule out high-grade lesions or cancer among HPV-positive women [21]. This is consistent with other areas in medicine in which screening for diseases, for example syphilis and HIV, is based on serial testing that uses a highly sensitive test first followed by a highly specific one to triage the resulting cases.

In addition to the above justification for a more rational use of HPV testing in conjunction with cytology, it also makes more public health sense in the era of HPV vaccination to create a surveillance system to monitor the epidemiology of HPV infection in the population. A system that would place HPV testing as the principal screening assay followed by cytology triage of HPV-positive women would have the added benefit of serving as a registry of HPV prevalence and associated lesions. With appropriate record linkage to vaccination registries and selective typing of HPV-positive cases, it would be possible to monitor the occurrence of incident HPV infection among vaccinated women, which would help determine the duration of vaccine efficacy in actual public health conditions. Current clinically approved HPV assays do not provide typing information, although this situation may change in the future because of the growing evidence that the oncogenic potential of HPV-16/18 may be substantially greater than that of other high-risk HPV types [12,13].

There are considerable logistical difficulties associated with the changes that the above proposed screening strategy entails, the most important of which is in personnel training. However, major restructuring to existing screening programmes are necessary regardless of the rationale for changing the order of tests described above. Simple maintenance of cytology-based programs as they exist today, with the added costs implied by large-scale vaccination, will place an enormous strain on the public health budget of any country. Given the transition phase prompted by the implementation of HPV vaccination, it makes public health sense to redesign screening programs from the ground up in light of the scientific knowledge base that has accumulated over the last decade. A restructuring based on the more cogent principles of screening with HPV and triaging with the Pap test places cytology in a more favourable light as the test that will ultimately determine management options for the HPV-positive woman. Moreover, when reading smears from such cases, cytotechnicians would not experience the fatigue and monotony that would unavoidably occur in a daily workload under conditions of low prevalence of abnormalities. Nearly every other smear would contain diagnostic elements that would elicit interest and keep the level of alertness high.

Disclosed potential conflicts of interest

ELF: Consultant (Digene Corporation, GenProbe, GlaxoSmithKline, Merck and Co., Inc.); Travel Support (Digene Corporation, GlaxoSmithKline, Merck and Co., Inc.); Research Grants (Merck and Co., Inc.)

JC: Consultant (Digene Corporation, GenProbe Inc., Roche, Norchip); Research Grants (Roche)

AH: Research Grants (GlaxoSmithKline)

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References

[1] Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. Lancet 2004;364(9447):1757–65.

[2] Villa LL, Costa RL, Petta CA, Andrade RP, Ault KA, Giuliano AR, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncol 2005;6(5):271–8.

[3] Mao C, Koutsky LA, Ault KA, Wheeler CM, Brown DR, Wiley DJ, et al. Efficacy of human papillomavirus-16 vaccine to prevent cervical intraepithelial neoplasia: a randomized controlled trial. Obstet Gynecol 2006;107(1):18–27.

[4] Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins CM, et al. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. Lancet 2006;367(9518):1247–55.

[5] Kulasingam SL, Myers ER. Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. JAMA 2003;290(6):781–9.

[6] Goldie SJ, Kohli M, Grima D, Weinstein MC, Wright TC, Bosch FX, et al. Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. J Natl Cancer Inst 2004;96(8):604–15.

[7] Taira AV, Neukermans CP, Sanders GD. Evaluating human papillomavirus vaccination programs. Emerg Infect Dis 2004;10(11): 1915–23.

[8] Benard VB, Eheman CR, Lawson HW, Blackman DK, Anderson C, Helsel W, et al. Cervical screening in the national breast and cervical cancer early detection program, 1995–2001. Obstet Gynecol 2004;103(3):564–71.

[9] Nanda K, McCrory DC, Myers ER, Bastian LA, Hasselblad V, Hickey JD, et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. Ann Intern Med 2000;132(10):810–9.

[10] Franco EL. Chapter 13: Primary screening of cervical cancer with human papillomavirus tests. J Natl Cancer Inst Monogr 2003;(31):89–96.

[11] Clifford GM, Rana RK, Franceschi S, Smith JS, Gough G, Pimenta JM. Human papillomavirus genotype distribution in low-grade cervical lesions: comparison by geographic region and with cervical cancer. Cancer Epidemiol Biomarkers Prev 2005;14(5):1157–64.

[12] Castle PE, Solomon D, Schiffman M, Wheeler CM. Human papillomavirus type 16 infections and 2-year absolute risk of cervical precancer in women with equivocal or mild cytologic abnormalities. J Natl Cancer Inst 2005;97(14):1066–71.

[13] Schiffman M, Herrero R, Desalle R, Hildesheim A, Wacholder S, Rodriguez AC, et al. The carcinogenicity of human papillomavirus types reflects viral evolution. Virology 2005;337(1):76–84.

[14] Zimet GD. Improving adolescent health: focus on HPV vaccine acceptance. J Adolesc Health 2005;37(suppl 6):S17–23.

[15] Zimet GD. Understanding and overcoming barriers to human papillomavirus vaccine acceptance. Curr Opin Obstet Gynecol 2006;18(suppl 1):s23–8.
[16] Riedesel JM, Rosenthal SL, Zimet GD, Bernstein DI, Huang B, Lan D, et al. Attitudes about human papillomavirus vaccine among family physicians. J Pediatr Adolesc Gynecol 2005;18(6): 391–8.
[17] Cuzick J, Clavel C, Petry KU, Meijer CJ, Hoyer H, Ratnam S, et al. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. Int J Cancer 2006.
[18] Ratnam S, Franco EL, Ferenczy A. Human papillomavirus testing for primary screening of cervical cancer precursors. Cancer Epidemiol Biomarkers Prev 2000;9(9):945–51.
[19] Mayrand MH, Duarte-Franco E, Coutlee F, Rodrigues I, Walter SD, Ratnam S, et al. Randomized controlled trial of human papillomavirus testing versus Pap cytology in the primary screening for cervical cancer precursors: design, methods and preliminary accrual results of the Canadian cervical cancer screening trial (CCCaST). Int J Cancer 2006;119(3):615–23.
[20] IARC Working Group. Cervix cancer screening. IARC handbooks of cancer prevention, Lyon: International Agency for Research on Cancer, World Health Organization, IARC Press; 2005.
[21] Cuzick J, Szarewski A, Cubie H, Hulman G, Kitchener H, Luesley D, et al. Management of women who test positive for high-risk types of human papillomavirus: the HART study. Lancet 2003;362(9399):1871–6.